REMARKS

The specification has been amended to correct the typographical and grammatical errors pointed out by the Examiner on page 3 of the Office Action mailed January 3, 2003 (Paper No. 15). The specification has also been amended to further clarify the description of Fig. 5. In particular, the description of Fig. 5 has been amended to conform to the graph presented in the figure and the text in Example 6 pertaining to Fig. 5. The amendments to the specification do not constitute new subject matter.

Claims 13, 15, 17, 19 and 26-37 were pending in this application. In order to expedite the prosecution of the present application and without conceding to the validity of the Examiner's rejections, Applicants have canceled claims 13, 15, 17, 19, 26 and 28-37 without prejudice to Applicants' right to pursue the subject matter in related applications, and have added new claims 38-71. Upon entry of this Amendment, claims 27 and 38-71 will be pending. The amendments and new claims are fully supported by the specification of the present invention (see, *e.g.*, page 11, line 3 to page 16, line 15, page 27, line 19 to page 33, line 15 and page 35, lines 2-4 of the specification), and do not constitute new matter.

Entry of the foregoing amendments and consideration of these remarks are respectfully requested.

1. NOTICE OF NON-COMPLIANT AMENDMENT

The Notice of Non-Compliant Amendment mailed on July 30, 2003 in connection with the application stated that the amendment filed in the U.S. Patent and Trademark Office on July 3, 2003 was found to be non-compliant with the Voluntary Revised Amendment Practice because the amendment did not contain a complete listing of all of the claims. In response to the Notice, Applicants submit this Revised Amendment which lists all of the claims in the application and their current status as called for by the Voluntary Revised Amendment Practice. Accordingly, Applicants respectfully submit that this Revised Amendment is in compliance with the Voluntary Revised Amendment Practice.

The Notice of Non-Compliant Amendment failed to indicate the deadline for responding to the Notice. In a teleconference on August 8, 2003 with Examiner Falk, she said that the box entitled "Amendment After Non-Final Action" on the Notice of Non-Compliant Amendment should have been checked, and thus, Applicants had one month to respond to the Notice of Non-Compliant Amendment with extensions of time under 37

C.F.R. § 1.113(a) being available. Accordingly, Applicants respectfully submit that this Revised Amendment is timely filed in the United States Patent and Trademark Office. Therefore, Applicants respectfully request entry and consideration of this Revised Amendment.

2. THE OBJECTIONS TO THE SPECIFICATION SHOULD BE WITHDRAWN

The Examiner has objected to the specification of the present application because of: (i) typographical and grammatical errors on page 3 of the specification of the present application; and (ii) lack of clarity in the description of Fig. 5. Applicants have amended the specification to correct the typographical and grammatical errors on page 3 of the specification and have clarified the description of Fig. 5 in view of the figure itself and the text in Example 6 pertaining to Fig. 5. Accordingly, the Examiner's objection to the specification is moot and should be withdrawn.

3. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

A. THE SPECIFICATION CONTAINS SUFFICIENT WRITTEN DESCRIPTION SUPPORT OF CLAIMS 26 AND 28-37

Claims 26 and 28-37 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner contends that the specification fails to provide sufficient written description for the chemical structure of a fragment, derivative or analog of IL-12 or 4-1BB ligand ("4-1BBL") that has the activity of the respective full length protein. For the reasons detailed below, Applicants respectfully assert that the rejection under 35 U.S.C. § 112, first paragraph, for lack of written description support cannot stand and should be withdrawn.

In order to expedite the prosecution of the application and without conceding to the validity of the Examiner's rejection, Applicants have canceled claims 13, 15, 17, 19, 26 and 28-37, without prejudice to Applicants' right to pursue the subject matter in related applications. Applicants have added new independent claims 38-41 and dependent claims 43-57, 59, 61, 63, 65, 67, and 69-71 to more particularly point and distinctly claim the invention. New independent claim 38 is directed to a method of treating cancer utilizing a nucleic acid molecule comprising a nucleotide sequence encoding IL-12 and 4-1BBL. New independent claim 39 is directed to a method of treating cancer utilizing a nucleic acid

molecule comprising a nucleotide sequence encoding a fragment, derivative or analog of IL-12 and 4-1BBL. New independent claim 40 is directed to a method of treating cancer utilizing a nucleic acid molecule comprising a nucleotide sequence encoding IL-12 and a fragment, analog or derivative of 4-1BB ligand. New independent claim 41 is directed to a method of treating cancer utilizing a nucleic acid molecule comprising a nucleotide sequence encoding a fragment, analog or derivative of IL-12 and a fragment, analog or derivative of 4-1BBL.

"If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, page 1106, Friday, January 5, 2001.

Applicants respectfully assert that the specification coupled with information well-known in the art as of the effective date of the present application would reasonably convey to one of skill in the art that Applicants were in possession of fragments, derivatives and analogs of IL-12 and 4-1BBL that retain the activity of wild-type IL-12 and wild-type 4-1BBL. The specification teaches that fragments, derivatives and analogs of IL-12 and 4-1BBL are functionally active and describes the activities of wild-type IL-12 and wild-type 4-1BBL (see, *e.g.*, page 2, lines 17-28, page 3, lines 25-31, and page 12, lines 28-36 of the specification). The specification also provides methods for assessing the activity of fragments, derivatives and analogs of IL-12 and 4-1BBL (see, *e.g.*, page 33, line 25 to page 34, line 15 of the specification). Moreover, methods for making and identifying fragments, derivatives or analogs of IL-12 and 4-1BBL that retain the activity of wild-type IL-12 and wild-type 4-1BB, respectively, were well-known in the art as of the effective date of the present application. Thus, Applicants respectfully assert that, given the state of the art and the information in the specification, the chemical structures of the fragments, derivatives and analogs of IL-12 and 4-1BBL recited in new claims 39-41 are sufficiently described to meet the written description requirements.

In view of the foregoing, Applicants respectfully assert that the rejection under 35 U.S.C. § 112, first paragraph, for lack of written description support cannot stand and should be withdrawn.

B. THE CLAIMS ARE ENABLED

Claims 13, 15, 17, 19, 26 and 28-37 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner contends that the specification fails to provide enablement for: (1) the chemical structure of any fragment, derivative or analog of IL-12 or 4-1BBL that has the function of IL-12 or 4-1BBL, respectively; (2) treating any type of tumor other than the solid tumors described in the working example; and (3) routes of administering IL-12 encoding nucleic acid molecules other than intratumoral administration, that will achieve an effective amount of the transgene at the target site. For the reasons detailed below, Applicants respectfully assert that the rejection 35 U.S.C. § 112, first paragraph, for lack of enablement cannot stand and should be withdrawn.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics, Inc.* 857 F. 2d 778, 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988). Enablement is not precluded even if some experimentation is necessary. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F. 2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). The Court of Appeals for the Federal Circuit has determined that experimentation, though laborious, is not undue experimentation where the specification provides a reasonable amount of guidance. *In re Wands*, 858 F. 2d 731 (Fed. Cir. 1988).

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstandt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation is "undue" since the term "experimentation" implies that the success of the particular activity

> is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original).

First, Applicants respectfully assert that the specification of the present application coupled with information known as of the effective filing date of the present application provides sufficient guidance to enable one of skill in the art to make and use fragments, derivatives and analogs of IL-12 and 4-1BBL to practice the claimed methods without undue experimentation. The specification of the present application teaches that fragments, derivatives and analogs of IL-12 and 4-1BBL are functionally active and describes the activities of wild-type IL-12 and wild-type 4-1BBL (see, *e.g.*, page 2, lines 17-28, page 3, lines 25-31, and page 12, lines 28-36 of the specification). The specification also provides methods for assessing the activity of fragments, derivatives and analogs of IL-12 and 4-1BBL (see, *e.g.*, page 33, line 25 to page 34, line 15 of the specification). Moreover, methods for making and identifying fragments, derivatives or analogs of IL-12 and 4-1BBL that retain the activity of wild-type IL-12 and wild-type 4-1BB, respectively, were well-known in the art as of the effective date of the present application. Thus, Applicants respectfully submit that the specification of the present application fully enables one of skill in the art to make and use the fragments, derivatives and analogs of IL-12 and 4-1BBL recited in new claims 39-41, without undue experimentation.

Second, Applicants respectfully assert that the specification of the present application coupled with information known as of the effective filing date of the present application provides sufficient guidance to enable one of skill in the art to treat any tumor, by administering the nucleic acid compounds by any route, without undue experimentation. As pointed out by the Examiner on page 8 of the Office Action mailed January 3, 2003 (Paper No. 15), the working examples in the specification of the present application demonstrate the therapeutic efficacy of IL-12 and 4-1BB ligand in the treatment of two different animal models for tumors, namely lung and hepatic tumor models (see, *e.g.*, Example 6, in particular page 42, lines 4-26). Applicants respectfully assert that they need not demonstrate the therapeutic efficacy of the claimed invention for each and every type of tumor, or for each and every route of administration. A specification that discloses at least one method for making and using the claimed invention enables the entire scope of the claims and satisfies the enablement requirement of 35 U.S.C. 112 (see MPEP 2164.01(b) citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970)). The specification of the present application

provides examples of the types of cancer that may be treated in accordance with the claimed methods and provides examples of the possible routes for administering the nucleic acid compounds recited in the claims (*see, e.g.*, page 27, lines 22-38 and page 35, lines 2-4 of the specification of the application). The specification of the application provides methods for assessing the therapeutic efficacy of the nucleic acid compounds recited in the claims for the treatment of cancer (see, *e.g.*, page 33, line 16 to page 34, line 22 of the specification of the application) and as of the effective date of the present application, methods for assessing the therapeutic efficacy of compounds for the treatment of cancer were well known. Thus, Applicants respectfully assert that one of skill in the art would be able to determine if the nucleic acid compounds recited in the claims were therapeutically effective for the treatment of a particular cancer using a particular route for administering the compounds without undue experimentation. Accordingly, Applicants respectfully submit that the specification of the present application fully enables one of skill in the art to practice the claimed methods without undue experimentation.

In view of the foregoing, Applicants respectfully assert that the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement cannot stand and should be withdrawn.

4. THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 13, 15, 17, 19, 26 and 28-37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Caruso *et al.*, 1996, *PNAS* 93:11302-11306 (hereinafter "Caruso") taken with Melero *et al.*, 1998, *Eur. J. Immunol.* 28:1116-1121 (hereinafter "Melero") and Vinay *et al.*, *Semin. Immunol.* 10:481-489 (hereinafter "Vinay"). The Examiner contends that: (1) Caruso teaches that the intratumoral administration of an adenovirus expressing murine IL-12 (Adv/m IL-12) into hepatic metastasis of a murine model of colon carcinoma results in decreased tumor volume for the mice and that this anti-tumor activity is mediated by the induction of IFN-γ; (2) Melero teaches that the use of a retroviral vector expressing 4-1BBL on P815 mastocytoma and AG104A sarcoma augments the immune response mediated by CD8+ CTL and results in associated specific tumor cell lysis; and (3) Vinay teaches that 4-1BB signaling in costimulating activated T-cells with soluble 4-1BBL results in IFN-γ secretion and influences various effector functions. The Examiner contends one of skill in the art of tumor cytokine therapy would have been motivated to combine the teachings of Caruso with the teachings of Melero and Vinay. The Examiner concludes that since both the functionality of IL-12 and 4-1BBL are related to the induction of IFN-γ secretion and both IL-12 and 4-1BBL have been demonstrated to have anti-tumor activity, it would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Caruso with the teaching of Melero to use both IL-12 and 4-1BBL for reducing tumor volume with decreased toxicity caused by IL-12 alone and with reasonable expectation of success. Applicants respectfully disagree.

A finding of obviousness requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1996). The proper inquiry is whether the art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Appellants' disclosure. *In re Vaeck* 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

Obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination", and "teachings of references can be combined only if there is some suggestion or incentive to do so." *In re Fine* 837 F.2d 1071, 1075 (Fed. Cir. 1988).

None of the cited references, alone or in combination, teach or suggest administering IL-12 encoding nucleic acids and 4-1BBL to treat cancer. Caruso provides that intratumoral administration of a recombinant adenoviral vector expressing murine IL-12 results in high level expression of IL-12 at the tumor site and induces a strong anti-tumor immune response in a well-established orthotopic murine colon carcinoma (MCA26) liver metastases model in syngenic Balb/c mice. Caruso also provides that supernatants from MCA 26 colon carcinoma cells transduced with Adv/mIL-12 induced IFN-γ release by splenocytes from naive Balb/c mice. Caruso does not mention 4-1BBL, much less methods for treating cancer by administering to a subject IL-12 encoding nucleic acid and 4-IBBL. Moreover, when Caruso speculates about combination therapy for the treatment of cancer, Caruso merely suggests combining Adv/mIL-12 with adenoviral vectors expressing murine IL-2 and thymidine kinase (Caruso at page 11305, second column last page). Thus, Caruso does not teach or suggest the claimed invention.

The deficiencies of Caruso are not cured by Melero or Vinay. Melero merely sets forth that mice inoculated with P815 tumor cells engineered to express 4-1BBL developed a strong CTL response and immunity against wild-type tumor cell rechallenge. Melero does

not mention IL-12, much less methods for treating cancer by administering to a subject IL-12 encoding nucleic acids and 4-1BBL. Moreover, when Melero speculates about combination therapy for the treatment of cancer, Melero merely suggests combining B7-1, a stimulator of the CD28 signaling pathway, with 4-1BBL since Melero's data indicates that the B7-CD28 interaction is required for optimal expression of 4-1BB on T-cells (Melero at page 1119). Thus, Melero does not provide a motivation to one of skill to combine its teaching with the teaching of Caruso to administer IL-12 encoding nucleic acids and 4-1BBL to treat cancer, much less a reasonable expectation of the success of such treatment. Accordingly, Melero does not teach, suggest or provide a motivation to one of skill in the art to practice the claimed invention.

Vinay is a review that generally describes 4-1BB and its role in the immune response. Vinay provides that the stimulation of 4-1BB stimulates the expression of secretion of a number of cytokines and that those cytokines vary depending upon the origin of the cells. For example, the stimulation of murine 4-1BB results in IL-2, IL-4 and IFN-γ synthesis, while the stimulation of human 4-1BB results only in IFN-γ secretion. Vinay does not teach, suggest or provide a motivation to one of skill in the art to administer IL-12 encoding nucleic acids and 4-1BBL to treat cancer, much less provide a reasonable expectation of the success of such treatment. There are a number of other cytokines including IL-2 which induce IFN-γ secretion. Moreover, the disclosure in Vinay that the administration of monoclonal antibodies to 4-1BB can completely eradicate established tumors would not motivate one of skill in the art to combine the disclosure of Vinay with the disclosures of Caruso (Vinay at page 486, second col., first full paragraph). Accordingly, Vinay, alone or in combination, does not teach, suggest to provide a motivation to one of skill in the art to practice the claimed invention.

In view of the foregoing, Applicants respectfully assert that the rejections under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

CONCLUSION

Applicants respectfully request that the foregoing amendments and remarks be entered and made of record in the present application. Withdrawal of all of the rejections and consideration of the amendments are requested. An allowance of the application is earnestly sought. If any issues remain, the Examiner is respectfully invited to telephone the undersigned.

Respectfully submitted,

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